CHRONIC TOXICITY SUMMARY

VINYL ACETATE

(1-acetoxyethylene; acetic acid, vinyl ester; acetic acid, ethenyl ester; VAC; vinyl A monomer; ethenyl ethanoate)

CAS Registry Number: 108-05-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**200 µg/m^3** (50 ppb)
Critical effect(s)	Nasal epithelial lesions in rats and mice
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1994)

Description	Colorless liquid
Molecular formula	$C_4H_6O_2$
Molecular weight	86.09 g/mol
Density	0.932 g/cm^3 @ 20°C
Boiling point	72.7° C
Melting point	–93.2°C
Vapor pressure	115 torr @ 25°C
Solubility	Slightly soluble in water, soluble in ethane, acetone, chloroform; >10% soluble in ethanol and benzene
Conversion factor	1 ppm = 3.52 mg/m^3 @ 25°C

III. Major Uses and Sources

The major use of vinyl acetate monomer is in the manufacture of polyvinyl and vinyl acetate copolymers, which are used in water-based paints, adhesives, paper coatings, and applications not requiring service at extreme temperatures (HSDB, 1994). It is also used in safety glass interlayers and in hair sprays (HSDB, 1994). In the atmosphere vinyl acetate breakdown can result in formation of acetaldehyde. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 3855 pounds of vinyl acetate (CARB, 2000).

IV. Effects of Human Exposures

Deese and Joyner (1969) conducted an occupational study of 21 chemical workers with a mean length of employment of 15.2 years and exposed to a time-weighted average of 8.6 ppm (30.3 mg/m^3) VA. No adverse effects were noted following chest x-ray, electrocardiogram, blood chemistry, and urinalysis. The control group (sample size unspecified) consisted of workers in

units not exposed to VA. Deese and Joyner (1969) also showed intolerable eye irritation in 3 out of 3 subjects exposed for an unspecified extended period of time to 21.6 ppm (76 mg/m^3) VA. Upper respiratory irritation was also experienced by a majority of 5 subjects. Odor was detected at 0.4 ppm (1.4 mg/m^3) in 3 out of 3 subjects.

V. Effects of Animal Exposures

A 104-week inhalation study in rats and mice (90/sex/group) was conducted using concentrations of 0, 50, 200, or 600 ppm (0, 176, 704, or 2113 mg/m^3) vinyl acetate (VA) (Owen, 1988). The study was later published by Bogdanffy *et al.* (1994). Exposures were for 6 hours/day, 5 days/week. Histology was performed on all major organs. There was no mortality resulting from these exposures. A close examination of the effects of VA on the lung and nasal passages showed significant lesions in the nasal cavity, bronchi, and lungs of rats exposed to 600 ppm VA. Lesions included olfactory epithelial metaplasia/atrophy (see table below) and nest-like epithelial folds in the nasal cavity, exfoliation of bronchial epithelium, fibrous intraluminal projections in the bronchi, and pigmented histiocyte accumulation in the lungs. Body weight gain of rats was significantly decreased in the 600 ppm VA group. Rats treated with 200 ppm VA showed some evidence of epithelial atrophy and metaplasia in the nasal cavity. No effects were observed in the rats exposed to 50 ppm VA.

Number of male rats with olfactory epithelial atrophy (Bogdanffy *et al*. 1994)

VA (ppm)	N in group	Very slight	Slight	Moderate	Severe
0	58	0	0	0	0
50	59	1	2	0	0
200	60	4	47***	2	0
600	60	0	7*	33***	10***

* $p<0.05$; ***$p<0.001$ by Fisher's pair-wise test compared to control group

Mice also exhibited significant histological lesions in the respiratory tract following exposure to 200 ppm VA or greater. The lesions included atrophy of the olfactory epithelium and submucosal gland. At 600 ppm, hyperplasia of the trachea was observed, in addition to exfoliation/flattening of the bronchial epithelium and decreased body weight gain. Relative brain and kidney weights were increased in the 600 ppm group at the end of the study, and absolute liver, heart and kidney weights were also significantly elevated. No adverse effects were observed in the 50 ppm group.

A 13-week study on the effects of VA in mice was conducted by Owen (1980a). Mice (10/sex/concentration) were exposed to 0, 50, 200, or 1000 ppm (0, 176, 704, or 3520 mg/m^3) VA for 6 hours/day, 5 days/week for 13 weeks. A concentration-dependent increase in the incidence of diffuse rhinitis, beginning at the 200 ppm concentration, was detected using histopathological examination. Focal pneumonitis was observed in the 1000 ppm treatment group. No adverse effects were seen in the 50 ppm treatment group. An identical study in rats was also conducted by Owen (1980b). In this study, body weight gain was significantly reduced in male and female rats exposed to 1000 ppm VA. An increase in the incidence of mild histiocytic alveolitis was observed in the 1000 ppm group.

Irvine (1980) conducted a study on the developmental toxicity of VA in rats. Groups of 24 pregnant female rats were exposed to 0, 52, 198, or 1004 ppm (0, 182, 696, or 3533 mg/m^3) VA for 6 hours/day on days 6-15 of gestation. Significant maternal toxicity, as measured by reduced weight gain from day 10 through day 15, was observed in animals exposed to 1004 ppm. Fetotoxicity, as measured by reduced crown-rump length, reduced body weight, and increased incidence of ossification defects in the sternebrae and occipital regions, was observed in the 1004 ppm group. No maternal or fetal effects were seen at the lower two VA treatments.

In another developmental toxicity study, groups of 23-24 Crl:CD(SD)BR rats were given 0, 200, 1000, or 5000 ppm VA in drinking water or exposed 6 hr/day to 0, 50, 200, or 1000 ppm VA on gestation days 6-15 of gestation. The authors (Hurtt *et al*., 1995) estimated that the doses by both routes were approximately 0, 25, 100, or 500 mg/kg/day. VA in the drinking water produced no evidence of maternal or developmental toxicity at any dose. In the inhalation study, maternal toxicity was indicated by a reduction in weight gain of dams exposed to 1000 ppm. Fetal toxicity was evident by a significant decrease in mean fetal weight and mean crown-rump length in fetuses from the 1000-ppm group and by a significant increase in the incidence of minor skeletal alterations (especially delayed ossification) in fetuses from dams exposed to 1000 ppm VA. These results indicated to the authors that VA is not uniquely toxic to the conceptus. The NOAEL was greater than 5000 ppm via the drinking water and 200 ppm by the inhalation route.

VI. Derivation of Chronic Reference Exposure Level

Study	Bogdanffy *et al*., 1994
Study population	Male and female Sprague-Dawley rats and CD-1 mice (90/sex/group)
Exposure method	Discontinuous inhalation exposures (0, 50, 200, or 600 ppm) over 104 weeks
Critical effects	Histological lesions of the nasal epithelium
LOAEL	200 ppm
NOAEL	50 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	104 weeks
Average experimental exposure	8.9 ppm for NOAEL group (50 x 6/24 x 5/7)
Human Equivalent Concentration (HEC)	1.4 ppm for NOAEL group (RGDR = 0.15 based on a gas with respiratory effects in both rats and mice)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.05 ppm (50 ppb, 0.2 mg/m^3, 200 μg/m^3)

The chronic REL is the U.S. EPA RfC (U.S. EPA, 1995) for vinyl acetate. Acetaldehyde, a hydrolysis product of vinyl acetate, was present in the Owen (1988) study at a concentration of 49 ppm (89 mg/m^3). The duration-adjusted concentration for acetaldehyde was 16 mg/m^3, whereas the NOAEL for histological lesions in rats by Appleman *et al.* (1982) was 48.75 mg/m^3 acetaldehyde. Therefore, the concentration of acetaldehyde was not considered to account for significant irritation in the Owen (1988) study. OEHHA accepted the U.S. EPA analysis.

For comparison, Irvine (1980) obtained a NOAEL of 198 ppm for fetotoxicity in rats exposed 6 hours/day on days 6-15 of gestation. This is equivalent to 50 ppm continuous exposure during development. Multiplying by an RGDR of 1 and dividing by a total UF of 30 (3 for interspecies and 10 for intraspecies) results in a REL estimate based on fetotoxicity of 1.7 ppm. The results of Hurtt *et al*. (1995) also yield an estimate of 1.7 ppm.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for vinyl acetate include the availability of controlled exposure lifetime inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathological analysis, and the observation of a NOAEL. The major area of uncertainty is the lack of adequate human exposure data.

VIII. Potential for Differential Impacts on Children's Health

Since the chronic REL (0.05 ppm) is lower than the comparison estimate based on developmental effects (1.7 ppm), the REL is likely to be protective of children. However, there is no direct evidence in the literature to quantify a differential effect of vinyl acetate in infants and children relative to adults.

IX. References

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